

0051

Lipid emulsions used in parenteral nutrition induce endothelial dysfunction in porcine coronary artery rings: role of oxidative stress and cyclooxygenase-derived vasoconstrictors

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Lipid emulsions are used to provide a source of calories and essential fatty acids for patients requiring parenteral nutrition. They have been associated with hypertriglyceridemia, hypercholesterolemia and metabolic stress, which may promote the development of endothelial dysfunction. The aim of the present study was to determine the possibility that five different commercial lipid emulsions affect the endothelial function of coronary arteries, and, if so, to investigate the underlying mechanism.

Porcine coronary arteries were incubated with lipid emulsions for 30 minutes before the determination of vascular reactivity in organ chambers and the level of oxidative stress using the redox-sensitive fluorescent dye dihydroethidium (DHE). Incubation of coronary artery rings with either Lipidem[®], Medialipid[®] or Smoflipid[®] (medium-chain triglycerides), but not with Intralipid[®] or Clinoleic[®] (long-chain triglycerides), significantly reduced the bradykinin-induced endothelium-dependent relaxations mediated by both nitric oxide (NO) and endothelium-dependent hyperpolarization (EDH). In contrast, Lipidem[®] did not affect endothelium-independent relaxations to sodium nitroprusside. The endothelial dysfunction induced by Lipidem[®] was significantly improved by indomethacin, a cyclooxygenase (COX) inhibitor, and by inhibitors of oxidative stress (N-acetylcysteine, superoxide dismutase, catalase) and transition metal chelating agents (neocuproine, L-histidine, desferoxamine). Lipidem[®] markedly increased the vascular oxidative stress as indicated by increased DHE signal throughout the arterial wall. The present findings indicate that several but not all lipid emulsions induce an endothelial dysfunction in coronary artery rings, involving both blunted NO- and EDH-mediated relaxations. The Lipidem[®]-induced endothelial dysfunction is associated with increased vascular oxidative stress and the formation of COX-derived vasoconstrictor prostanoids.

0104

Blackcurrant juice prevents endothelial dysfunction and vascular oxidative stress in the mesenteric artery of cirrhotic rats with hepatopulmonary syndrome

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The aim of the present study was to determine whether the ingestion of a polyphenol-rich Blackcurrant juice (PRBJ) improves the endothelial dysfunction and vascular oxidative stress in the chronic bile duct ligation (CBDL) rats, an experimental model of hepatopulmonary syndrome (HPS), one of the serious complications of liver cirrhosis. Male Wistar rats received either control drinking water or water containing a 60 mg/kg of PRBJ for 7 weeks. After 3 weeks, the rats underwent either ligation and resection of the common bile duct (CBDL) or sham surgery (sham). Vascular reactivity was assessed in organ chambers, the expression level of proteins by immunofluorescence, and the vascular formation of reactive oxygen species by dihydroethidine. Plasma levels of pro-inflammatory cytokines were evaluated by flow cytometry. Both the nitric oxide (NO)- and the endothelium-dependent hyperpolarization (EDH)-mediated relaxations in mesenteric rings were significantly reduced in CBDL compared to sham. Impaired endothelium-dependent relaxations were associated with a reduced vascular expression of connexin 37 (Cx37) and small conductance calcium-dependent K⁺ channels (SK_{Ca}), and an increased expression of eNOS. In aortic sections of CBDL, an increased vascular oxidative stress and expression of NADPH oxidase subunits was observed. The endothelial dysfunction in CBDL was significantly prevented by PRBJ, and this effect was associated with the normalization of the vascular expression of

Cx37, SK_{Ca}, and eNOS. PRBJ treatment also reduced vascular oxidative stress in the aorta, and the increased plasma level of pro-inflammatory cytokines in CBDL.

Altogether, these results indicate that PRBJ ingestion prevented the blunted NO- and EDH-mediated endothelium-dependent relaxation in the mesenteric artery of CBDL most likely by preventing the excessive oxidative stress in the arterial wall.

0033

Sweet beverages-related acute hyperglycemia and vascular nitric-oxide endothelial dysfunction: can exercise training be a preventive strategy?

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The main objective of our study was to explore the effects of sweets beverages-related acute hyperglycemia (HG) on vascular endothelial function and the potential role of nitric oxide (NO) signaling pathway in macro- and micro-circulation vascular beds. As several investigators reported that exercise improves NO pathway and endothelial function, we also examined whether regular moderate physical activity could protect vascular endothelial function during hyperglycemia. Laser Doppler blood flow measurements associated to transcutaneous iontophoresis of vasoactive drugs was used to evaluate endothelial function in vivo i) in normoglycemic condition (NG) and ii) during an acute hyperglycemic stress (2g/kg of glucose, i.p.; HG). Ex vivo, endothelial function was evaluated on isolated rat aortic rings before and after an hyperglycemic stress (2h, glucose 30mM). The potential role of oxidative stress and NO pathway were evaluated i) pharmacologically by the use, in-vivo, of a non specific antioxidant (N-Acetylcysteine, NAC), or of the eNOS cofactor tetrahydrobiopterin (BH4), and ii) with the evaluation of the endothelial NOSynthase (eNOS) activation state (phosphorylation at ser1177) by western blot. In response to HG an altered endothelium-dependent vasodilation was markedly obvious in microcirculation and to a lesser extent in macrocirculation. Oxidative stress and alteration of the coupling state of eNOS seem to be involved in such result, since the use of NAC or BH4 prevented HG-induced alteration of endothelial function. However, acute hyperglycemic stress has no effect on eNOS phosphorylation state. Finally, chronic aerobic exercise (70% maximal aerobic velocity, 5days/week for 5 weeks) was able to prevent the deleterious effect of HG stress on endothelial function. To conclude, we demonstrated here that in vivo acute HG-related endothelial dysfunction seems to be explained by nitro-oxidative stress, and could be prevented by moderate exercise training.

0042

The Crataegus extract WS1442[®] retards replicative endothelial senescence by preventing eNOS down-regulation: role of NADPH oxidase- and COX-mediated redox-sensitive expression of p53/p21 and p16

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Endothelial cell senescence promoting endothelial dysfunction has been suggested to contribute to the development of age-related vascular disorders. Endothelial senescence is characterized by an irreversible cell cycle arrest involving the p53/p21 and p16 pathways, oxidative stress and down-regulation of endothelial nitric oxide synthase (eNOS). The present study has evaluated whether the Crataegus special extract WS1442[®], a rich source of polyphenols and a potent activator of eNOS, prevents replicative senescence in cultures of porcine coronary artery endothelial cells, and, if so, to elucidate the underlying mechanism. Replicative senescence was induced by sequential passaging of primary cultures of endothelial cells up to the fourth passage (P4). Senescence was assessed using senescence-associated β -galactosidase (SA- β -gal) activity, the formation of reactive oxygen species (ROS) using dihydroethidine (DHE) by flow cytometry, and the level of protein expression by Western blot analysis. Passaging of cultures of endothelial cells was associated with a gradual increase in the SA- β -gal activity, the DHE signal and the level of p53, p21 and